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Man-made mineral fibers and lung cancer

Epidemiologic evidence regarding the causal hypothesis

by Olli S Miettinen, MD, PhD,[1] Charles E Rossiter, MA, FFOM[2]

MIETTINEN OS, ROSSITER CE. Man-made mineral fibers and lung cancer: epidemiologic evidence regarding the causal hypothesis. *Scand J Work Environ Health* 1990;16:221—31. Reviews of the epidemiologic literature point to a causal connection between lung cancer and exposure to airborne man-made mineral fibers. The present critical re-review starts with the requirements for epidemiologic evidence to be informative regarding a hypothesis on cancer etiology. The previous reviews relate lung cancer mortality to exposure that is too recent to be relevant. The relation to relevant (distant) exposure in the available data involves notable confounding by coexposure to other agents in the work environment, by the lower socioeconomic status of the exposed workers, and possibly by smoking. Moreover, analyses of trends in standardized mortality ratios according to timing and duration of exposure involve a lack of mutual comparability between the ratios. Given these problems, the available evidence is inadequate for testing the causal hypothesis. However, reanalyses of the available data, augmentation of the data with reanalyses, and new studies could eliminate the existing inadequacies.

Key terms: epidemiologic methods, glass wool, lung cancer, meta-analysis, mineral fibers, rock wool, slag wool, standardization of rates.

With the use of asbestos soon to be banned in the United States, and its use already banned in some other countries, on the grounds that asbestos causes lung cancer, the safety of other fibers, including man-made mineral fibers (MMMF), has become a major issue in public health.

Current epidemiologic evidence on the effect of MMMF exposure on the risk of lung cancer has undergone several authoritative reviews, the most eminent among them being the following: (i) Sir Richard Doll's overview (1) of the epidemiologic papers presented at the third international symposium organized in 1986 on the safety of MMMF by the World Health Organization's (WHO's) Regional Office for Europe, the International Agency for Research on Cancer (IARC), and the Joint European Medical Research Board (JEMRB) in association with the Thermal Insulation Manufacturers' Association of America (TIMA) (2), (ii) volume 43 (1988) of *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans,* devoted to MMMF and radon (3), and (iii) *Environmental Health Criteria,* number 77, "Man-Made Mineral Fibers," published in 1988 by the International Programme on Chemical Safety (IPCS) under the joint sponsorship of the United Nations Environmental Programme, the International Labour Organisation, and WHO (4).

Sir Richard Doll concluded that "an occupational hazard of lung cancer has been demonstrated in the rock and slag wool section of the industry and possibly in the glass wool section [p 805]." This conclusion presumably refers to effects of the fibers themselves rather than to the occupations per se (with unspecified alternatives). The IARC monograph, in turn, concluded that there is "limited evidence" (ie, suggestive but not definitive evidence) for rock-slag wool and "inadequate evidence" (ie, the evidence cannot be interpreted) as to the carcinogenicity of glass wool and glass filaments in humans. Finally, the IPCS report summarized the epidemiologic evidence by observing that "there have been indications of increases in lung cancer... mainly in workers in the rock wool/slag wool sector employed in an early production phase," but it noted that "it is possible that other factors may have contributed to this excess [p 18]." It also pointed out that "available data are consistent with the hypothesis that it is the airborne fiber concentrations that is the most important determinant of lung cancer risk [p 18]," independent of the type of fiber.

Even though these reviews are indisputably authoritative, their conclusions leave reason for confusion and skepticism. The conclusions from the separate reviews are not in accord with one another; in particular, the larger the group of experts conducting the review, the less compelling the evidence seems to be. More importantly, while these reviews are long on

[1] Department of Theory of Medicine, Free University, Amsterdam, The Netherlands, and Department of Epidemiology and Biostatistics and Department of Medicine, McGill University, Montreal, Quebec, Canada.

[2] Unit of Environmental and Occupational Health, London School of Hygiene and Tropical Medicine, London, England, and Joint European Medical Research Board.

Reprint requests to: Professor OS Miettinen, Department of Epidemiology and Biostatistics, McGill University, 1020 Pine Avenue W, Montreal, Quebec H3A 1A2, Canada.

describing the evidence, they all are short on evaluating it.

Given the state of the currently available major reviews, together with the widespread exposure to MMMF products and the attendant major public health interest in their safety, it is the purpose of this paper to (i) delineate the requirements to be met in order for epidemiologic research to be informative about the qualitative question of whether exposure to airborne MMMF causes lung cancer, (ii) examine the extent to which currently available epidemiologic studies satisfy the criteria for informativeness and what, therefore, the evidence from them means, and (iii) make recommendations for future epidemiologic studies on this topic. Whether the MMMF industry represents a health hazard to its workers in terms of exposure other than the fibers themselves is not a concern in this review.

This examination of the particular topic of the risk of lung cancer in relation to the inhalation of MMMF may also serve a larger purpose by bringing the prevailing principles of epidemiologic research on occupational cancer risks in general into critical focus. It may help stimulate reflection on and discussion of these questions and thereby help the development of a considered consensus on what the core principles should be.

REQUIREMENTS FOR INFORMATIVENESS

Evidence from a set of studies is informative in supporting or refuting a hypothesized causal connection if it is of relevant form and if, in addition, its empirical content is reasonably valid and reasonably precise.

Relevance of form

As to the form of evidence in the context of a causal hypothesis about cancer risk for humans, a first requirement for direct relevance is, naturally, that it address the human domain, that is, experience in humans. In this domain, it must represent incidence of the cancer's inception in relation to antecedent exposures to the agent in question. In practice only a proxy for the actual inception can be addressed — the diagnosis of the cancer or death from it. The exposures need to be defined in reference to particular time intervals backward from the time of outcome classification (case-noncase), specified with a view to possible time lags from exposure to effect on the outcome. Thus concern for a single agent may lead to the consideration of several lag-specific exposures (5, pp 226—227). Finally, the relation of incidence to any given (lag-specific) exposure must be conditional on all extraneous determinants of the incidence/risk (and fatality perhaps) of the cancer at issue, that is, on potential confounders of the relation.

Validity of content

For the empirical content of a relevant form to be valid (free of bias) for direct testing of a hypothesis of cancer causation in man, the following criteria must be met (5):

1. The definition of the study base (the population-time for cancer incidence/mortality) must be unbiased. In the context of a retrospective (segment of a) study base, therefore, the occurrence of the outcome event itself (here death from lung cancer) or latent determinants of its risk (imminence perhaps) should have no bearing on entry into membership in the study population or, if such a tendency exists, it should be unrelated to exposure history. The same requirement applies to terminations of contributions to the study base, whether retrospective or prospective.

2. Case identification (in the study base, for rate numerators) must be reasonably accurate, and any inaccuracies (false positive and false negative rates) should be unrelated to the relevant exposure histories.

3. Selection into study base representation (for rate denominators), in the context of sampling or incomplete census, should be unrelated to the exposure histories.

4. Information on exposure histories (for cases and base representatives) must be reasonably accurate (in relation to the true range of exposure), and any inaccuracies should be unrelated to the outcome status (case-noncase).

5. Potential confounding must be either shown to be absent in the study base, or else the confounders must be accurately measured and controlled in the analysis.

Especially because of the requirement that all potential confounders be known a priori and that, among them, all actual confounders be identified and measured with perfect accuracy, perfect validity of evidence for testing causal hypotheses is not attainable in nonexperimental research. Even in the face of imperfections, however, a study can be reasonably valid. Thus, an ostensibly "positive" study does in fact support the causal hypothesis if imperfections of validity can be deemed to explain at most a moderate proportion of the empirical relation between the outcome incidence and exposure. Similarly, an ostensibly "negative" study does in fact take away from the credibility of the hypothesis if it remains "negative" upon sufficient correction of the empirical relation for probable bias. In general, then, bias in nonexperimental research does not make it meaningless but requires adjustment of the statistical evidence for the bias, for its probability distribution (subjective).

Precision of content

In the context of a "positive" study, statistical evidence is reasonably precise for hypothesis testing if the null P-value (bias-corrected) is reasonably small (eg, <0.05) in conjunction with a point estimate (bias-corrected) representing a credible magnitude of the hypothesized relation. (See page 112 of reference 5.) In the context of "negative" evidence, the corresponding requirement is that the confidence interval (eg, 95 %) for the parameter of relation (eg, standardized mortality ratio) be reasonably narrow (around the null value, upon allowance for bias) and cover only immaterial deviations from the null value.

INFORMATIVENESS OF AVAILABLE EVIDENCE

Studies considered

All three of the reviews noted in the introduction focused on three studies whose "observations include the vast majority of those that have been reported on MMMF production workers in the past [p 806]" (1). These studies, described in the same volume that contained the Doll review, are referred to in our review as the European (6), the American (7), and the Canadian (8) studies.

Our review also focuses on these three main studies in such terms as they were reported to the 1986 symposium in Copenhagen (6—8). For further insight into the European study, a convenient source is a supplement of the *Scandinavian Journal of Work, Environment & Health* (9) dedicated to that study.

Relevance of form

The evidence from all three studies addresses experience in the human domain and in it the incidence of death from lung cancer in relation to exposure to airborne MMMF decades earlier (and also in relation to more recent exposure of dubitable relevance). To this extent the evidence from all three studies is (in part) clearly relevant to the testing of the causal hypothesis.

Whether this relation was considered conditionally on all potential confounders of substantial relevance is, by contrast, unclear at best. (See the section on confounding that comes later.)

Validity of content

Study base definition

In each of the three studies, the essence of the study base was the same, consisting of the course over time of a closed population (cohort) of exposed workers together with that of an open (dynamic) "general population," representing nonexposure. The exposed cohort consisted of persons with a record of past employment of some duration (in some plants a minimum of one year) in MMMF production, and the exposed segment of the study base was considered to consist of the cohort's retrospective course from the attainment of the minimum required duration of employment, together with a prospective segment. The unexposed segment of the study base consisted of "the general population's" (geographically matched) course in the span of calendar time involved in the exposed segment of the study base.

As for potential bias in the definition of the retrospective segment of the study base, the main question is whether, at the time of cohort formation (in the 1970s), the availability of previous (retrospective) records of employment in MMMF production bore any relation to interim deaths from lung cancer; for, if it did, the dependence was clearly differential between the exposed and unexposed populations. This matter has been addressed in earlier reports, which are very reassuring, especially in regard to the American study.

Another issue in possibly differential entry into the compared populations is that entry into MMMF production work implies absence of imminent death from lung cancer, whereas entry into (continuing membership in) "the general population" does not. Whereas this difference — conducive to "the healthy worker effect" (5, pp 32—33) — unquestionably existed in the earliest years, it must have disappeared after the minimal lag time required for any effect of exposure on the risk of death from lung cancer (10, 11).

Every effort to avoid bias from differential terminations of the contributions to the study base was made in all three studies, both retrospectively and prospectively, to trace the members of the exposed cohort to either death, emigration from the country, or the common closing date. Where these attempts failed, contributions were considered to have been terminated at an unspecified time (6), the "date of last observation" (7), or the common closing date (8). The treatment of these failures was a minor issue, since their frequency was less than 4 % in all three studies. In the unexposed populations, contributions to the study base terminated, naturally, by death, emigration from the country or region, or the common closing date. Overall, then, no appreciable differential terminations occurred between the contributions to the exposed and unexposed segments of the study base.

Case identification

In all three studies, case identification was based on death identification and the stated cause of death (lung cancer) on the death certificate. For lung cancer this procedure can be taken to be reasonably, but by no means totally, accurate, especially in earlier periods of calendar time. Thus the question is whether its inaccuracy was differential between the exposed and unexposed populations.

The exposed populations in these studies consisted mostly of unskilled laborers (12), in contrast to the unexposed "general population." If low socioeconomic status implied less accurate diagnosis or less accurate recording of lung cancer as the cause of death, then the studies involved incomparability of case identification, likely in the direction of relative underidentification among the exposed. In addition, incomparability with respect to the classification of death certificates, which were examined for the exposed but not for the unexposed, could have been a source of incomparability, likely in the direction of relative underidentification among the unexposed. The reports (6—8) do not address these issues, and therefore comparability with respect to the identification of cases of lung cancer death remains unclear.

An added point of some note is that, in the European study, cases were not identified at all in some segments of time and place of the unexposed experience: "National mortality reference rates have been extrapolated back to the date of starting MMMF production when this date is prior to the availability of rates [p 605]" (6). To the extent that this procedure introduced inaccuracy, it is obviously differential between the exposed and unexposed populations. On the other hand, this problem is again reduced or perhaps even obviated when one focuses on outcome experience sufficiently distant from initial exposure.

Study base representation

Validity of the representation of the study base (as for exposure history, etc) was not a problem, given the census approach to both the exposed and the unexposed segment of the study base.

Exposure histories

Exposure histories were superficially implicit in the definitions of the compared populations — the "exposed" cohort and the "unexposed" dynamic population — in each study, with equal clarity for cases and noncases. Therefore, in this superficial sense they are inherently comparable between cases of lung cancer death and representatives of the study base (noncases).

The core question is, however, whether, within the cohort, information about exposure histories was obtained in a comparable manner for the cases and noncases of lung cancer death. The information was drawn from employer's records made at the earlier time, and comparability may therefore be presumed.

The remaining issue is whether the compared populations represent an appreciable contrast in the true level of exposure. Of this possibility, again, there is little question in reference to exposure that occurred early enough to allow for a sufficient lag time to death from lung cancer.

Confounding

The question of whether the study base in each of these studies was free of confounding involves, as in any study of the effects of environmental exposure, two component issues between the index (exposed) and reference (unexposed) experiences, namely, comparability of *effects* and comparability of *populations*. (See sections 2.3.1—2.3.2 of reference 5.)

In this instance, comparability of effects is a matter of comparability of *work* between MMMF production on the one hand and the entire spectrum of other types of work (including none) in "the general population" on the other in respect to coexposures conducive to lung cancer.

Comparability of populations, in turn, is a matter of comparability of *workers* between MMMF production on the one hand and the entire spectrum of other types of work (including none) on the other — in respect to nonwork characteristics relevant to the risk of lung cancer.

Comparability of effects. The possibility of confounding by coexposures in the MMMF production environment was a serious threat to the validity of the studies in question. Work in the furnace area entailed the possibility of exposure to appreciable concentrations of polycyclic aromatic hydrocarbons (including benzpyrene), arsenic oxides, noxious fumes from pitch and tar binders, and asbestos (13); and in the main production area, "various binders, especially those of asphalt or tar type, probably contributed as well [p 543]," and "when resin binders were introduced, the curing ovens frequently ... leaked their gases to the production area [p 543]" (13).

The report of the European study states that "no effects could be attributed to other potential risk factors: use of bitumen binders, use of asbestos, exposure to formaldehyde [p 603]." But it is to be noted that failure to discern the effects of these, or any other, a priori relevant coexposures is no justification for ignoring their effects on the results.

The American report states that "we do know that for the mineral wool plant with the next to highest respiratory cancer excess (plant 7) the slag used was received from a copper smelter that smelted a very high content arsenic ore [p 652]." An earlier report from the American study (14) also noted "the possibility that asbestos was used in the mineral wool plants [p 3]," which was likely substantial for plants 13 (personal communication, J Hernan) and 17 in particular (15, 16). Yet these plants were not excluded from the study, nor was any allowance made for the effects of coexposures. Consonant with this, the recent report (7) concludes by noting that, "On balance, our findings... throw little light on the question of whether (the observed association) is due to the fibers themselves or is related to other contaminants that might be present

in the environment of man-made mineral fibre workers [p 653]." (The reader may ask why, then, is such research done at all.)

In the Canadian report, not even an allusion is made to the possibility of incomparability of extraneous effects.

Comparability of populations. All three studies accounted for the implications of age, sex, calendar time, and geographic region of residence.

Other concerns expressed in the reports are confined to the possibility of confounding by smoking habits. The European report acknowledged that "the absence of information on smoking habits is certainly a limitation [p 619]," but it expressed the (unsubstantiated) belief that "smoking is unlikely to explain the entire excess [p 619]" of lung cancer deaths among MMMF workers. In the American study, "smoking histories were obtained through telephone interviews with the worker himself (if still living) or a knowledgeable informant, ideally a member of the worker's immediate family." With this approach to history-taking, in the context of a third of the subjects being dead, and with "ever-smoked defined as 20 packs of cigarettes or more during a lifetime or a cigarette a day or more for 1 yr. or more [p 646]," the proportions of "ever-smoked" were compared, in three (broad) categories of age, with those in the white male population of the United States in 1980. The proportions were similar, but the methods by which they were derived were, alas, far from comparable, to say nothing about the superficiality of the contrast itself. In addition, in a regression analysis within the cohort, smoking was "controlled" in terms of "ever-never-smoked" and, separately, in terms of "duration of smoking and time since started smoking." This procedure does not, however, accord with the requirements for valid control of potential confounders. (See the Validity of Content section under Requirements for Informativeness.) The Canadian report, addressing the standardized mortality ratio (SMR) (=200, based on 19 cases) for lung cancer among "plants-only" workers, noted that: "Even though data on smoking are not available, such an increase is probably too large to be attributable solely to this cause [p 661]."

With all this attention to potential confounding by smoking habits specifically, none of the reports even alludes to the possibility of confounding by the nonspecific factor of *socioeconomic status.* Exposed workers in MMMF production are, as was noted already, mostly unskilled laborers (12) and thus generally of a lower socioeconomic status than "the general population." A lower socioeconomic status for the exposed cohorts implies, quite possibly for reasons that go beyond smoking, the expectation of elevated SMR values for lung cancer in particular (11, 17—19), as is illustrated in table 1.

Apart from the exposure-nonexposure contrast, all three studies sought additional evidence by exploring possible trends in the SMR values for lung cancer according to the time lag since the beginning of exposure, and also according to the duration of exposure. In this pursuit, all three studies involved the (implicit) presumption that SMR values for various lag times, and durations, were mutually comparable. Yet the ordinary SMR statistic involves only internal standardization, not mutual standardization. (See page 271 of reference 5 and the later section on SMR reanalyses of this review.) The longer the lag time, or the duration, the more the mortality experience on which the SMR is based is weighted in favor of older people. Thus the trend in SMR over age reflects, in part, age modification of the observed-to-expected ratio, and, in this context, it is important to note that the excess in the SMR for lung cancer among workers of lower socioeconomic status or the SMR excess arising from confounding by socioeconomic status shows a trend, a declining one, over age (table 1). Apart from age, the SMR values for different time lags since first exposure and for different durations of exposure are also devoid of mutual standardization as to calendar time (as well as to sex and geographic region).

A related problem in these analyses in the way they were carried out has to do with the "healthy worker effect" associated with continuing work. The longer the duration of exposure, the more likely the worker is to have been employed not only early in life, but recently as well, and this is the case in particular when duration is considered conditionally on the lag time since the onset of exposure. The consequence is that the healthy worker effect from recent employment tends to bring down the SMR for persons exposed long-term, or even to create an "inverse relationship" such as was observed in the American study.

Table 1. Standardized mortality ratios[a] for all causes of death and for respiratory cancer among manual workers in Great Britain in 1979—1980 and 1982—1983 combined, by level of skill and age (18).

Cause of death	Age[b] (years)	
	45—54	55—64
Any		
Skilled workers	105	110
Semi-skilled workers	117	115
Unskilled workers	181	153
Respiratory cancer		
Skilled workers	115	120
Semi-skilled workers	133	122
Unskilled workers	204	169

[a] Ratios (multiplied by 100) of observed numbers of death in the occupational subpopulations to their respective expected numbers, the latter being based on the total population rates specific for age and sex.

[b] Data for persons over 65 years of age were not available from the source; data for persons under 45 years of age were not relevant in the context of lag times of ≥20 years.

Table 2. Observed (O) and expected (E) numbers of deaths from lung cancer ≥20 years after first exposure, by type of man-made mineral fiber (MMMF).

Type of fiber	Study						Total	
	European		American		Canadian			
	O	E	O	E	O	E	O	E
Any MMMF	80	67.9	301	268.0	12	6.2	393	342.1
Slag (±rock) wool	23	12.2	45	34.4	—	0.0	68	46.6
Rock wool only	11	12.1	—	0.0	—	0.0	11	12.1
Glass fibers only	46	43.6	256	233.6	12	6.2	314	283.4
Fine fibers (±wool/filaments)	—	0.0	14	10.7	—	0.0	14	10.7
Wool (±filaments) without fine fibers	46	41.3	193	176.3	12	6.2	251	223.8
Filaments only	—	2.3	49	46.6	—	0.0	49	48.9

Table 3. Estimates of the standardized mortality ratio (SMR) for lung cancer ≥20 years after first exposure, by type of man-made mineral fiber (MMMF). (95 % CI = 95 % confidence interval)

Type of fiber	SMR	
	Point estimate	95 % CI
Any MMMF	115	104—127
Slag (±rock) wool	146	113—183
Rock wool only	91	45—153
Glass fibers only	111	99—123
Fine fibers (±wool/filaments)	131	71—208
Wool (±filaments) without fine fibers	112	99—126
Filaments only	100	73—128
Any MMMF other than slag wool	110	98—122

Proper analyses of these matters would accent, or perhaps be confined to, those employed over 20 years ago, say, irrespective of subsequent employment. In this domain, as was already noted, the healthy worker effect will have vanished (11), and the SMR values may be related to the amount of etiologically relevant exposure, for example, to the amount of exposure over 20 years ago. In none of the studies was this procedure carried out.

Precision of content

A simple yet commonly adequate index of the precision of an epidemiologic cause-effect study is the number of exposed cases (5, p 97), observed and/or expected. This index is applicable not only to individual studies but, just as readily, to meta-analysis of a whole series of studies reported in the literature.

Before this number can be addressed properly in studies of cancer etiology, it is again necessary to appreciate the minimum lag time from exposure to outcome. Especially when the lag from the inception of exposure to death from lung cancer is under consideration, the accent must be on cases exposed more than, say, 20 years ago if relevance is to be assumed.

The observed/expected numbers of exposed cases, in the sense of a lag time of at least 20 years from the initial exposure and with all types of exposure combined, were 80/67.9, 301/268.0, and 12/6.2 in the European, American, and Canadian studies, respectively, adding up to the total of 393/342.1, numbers shown in table 2. The table also shows the corresponding numbers specific to particular types of exposure (slag wool with or without rock wool, rock wool only, fine glass fibers with or without glass wool, glass wool with or without glass filaments but without fine fibers, and glass filaments only).

The SMR values specific to the three main types of fiber (slag, rock, and glass) (table 3) do not show statistically significant deviations from homogeneity; the chi square (2 degrees of freedom) for their homogeneity is $4\{[(68)^{1/2}-[46.6(1.15)]^{1/2}]^2+[(11)^{1/2}-[12.1(1.15)]^{1/2}+[(314)^{1/2}-[283.4(1.15)]^{1/2}=4.6$, corresponding to $P=0.1$. In this statistic, the value 1.15 represents the overall observed-to-expected ratio across the three types of exposure, involving $68+11+314=393$ observed cases and the expected number of $46.6+12.1+283.4=342.1$, so that $SMR=100(393/342.1)=115$ (table 3). On the other hand, the SMR for slag wool (notable for its relevant coexposures) is significantly higher than that for the union of rock and glass wool: $X^2=4.1$, $P=0.02$ (one-sided).

The SMR values for the three types of glass fiber (table 3), similarly, do not show statistically significant deviations from homogeneity ($X^2=0.92$, $P=0.6$), nor is the SMR for fine fibers significantly higher than that for the union of the other two types of glass fiber ($X^2=0.37$, one-sided $P=0.2$).

Thus the primary interest is in the overall SMR over all types of fiber other than slag wool. For it, the point estimate is $325/295.5=110$, associated with the 95 % confidence interval (5, p 138) of $[(325)^{1/2}\pm1.96(0.5)]^2/295.5=98$—122 (table 3).

Overall informativeness

Whereas on the surface the statistical evidence suggests a slight elevation of lung cancer risk from exposure (over 20 years ago) to airborne MMMF at large and from exposure to slag wool specifically, these suggestions lose meaning upon allowance for definite, positive confounding by extraneous agents in the workplace of MMMF workers and by socioeconomic status. In fact, in the light of the effect of socioeconomic status alone (table 1), the observed SMR values (table 3) are remarkably *low,* even if full assessment of this aspect would require availability of data of the sort given in table 1 for higher ages.

Even upon allowance for these two types of confounding, however, interpretation of the evidence as either supporting the hypothesis, or detracting from it, would require assurance of absence of confounding by smoking, and the studies provide either no or noncompelling evidence in this respect.

No assessment of possible trend in the SMR in relation to the duration of exposure (over 20 years ago), with maintenance of comparability with respect to such variables as age, can be made from the published data.

RECOMMENDATIONS FOR FUTURE STUDIES

Recommended future studies consist of (i) reanalyses of the data now available from the three studies, (ii) augmentation of the data from the three studies, with analyses analogous to the reanalyses, and (iii) new study/studies resulting from a request for proposals.

Reanalyses of the existing data

Reanalyses of the existing data should be of two kinds, SMR analyses and regression analyses.

SMR reanalyses

SMR reanalyses should involve stratification by age (eg, lustra), calendar time (eg, decades), and geographic region (local), as before.

Within such strata, contributions to the amounts of population-time and the numbers of cases (observed and expected) should be restricted by the exclusion of women and persons with less than one year of employment. (See reference 1.) In addition, persons representing known and appreciable occupational exposure (over 20 years ago) to extraneous airborne agents known to be causal for lung cancer and persons first employed less than 20 years ago should not contribute. Notable among those exposed to extraneous agents are workers in plants 7, 13, and 17 in the American cohort and the preproduction workers exposed to asbestos in one of the Norwegian plants in the European cohort (1).

After such exclusions, the population-time and numbers of cases (observed and expected) within the strata should be derived primarily in reference to exposure more than, say, 20 years prior to any moment at which the contribution is made, with only secondary attention to more recent exposure.

A first set of analyses should address distant exposure in all-or-none terms and lead to separate SMR values for each of the following: (i) any appreciable exposure to any type of MMMF, (ii) any appreciable exposure to slag wool, with or without exposure to other types of MMMF, (iii) any appreciable exposure to rock wool only, (iv) any appreciable exposure to fine glass fibers, with or without exposure to glass wool, (v) any appreciable exposure to glass wool, with or without exposure to glass filaments but without exposure to fine glass fibers, (vi) any appreciable exposure to continuous glass filaments only. In essence, these analyses will replicate the results in the section on precision of content under Informativeness of Available Evidence, though with enhanced validity arising from the aforementioned exclusions.

The main concern in the reanalyses is to learn whether the SMR values for various amounts of exposure (in the distant time period) show an increasing trend over increasing amount, upon maintenance of comparability of the SMR values in terms of the stratification factors. The amounts of exposure in that time period should address each of the qualitative types of exposure that have been delineated in the preceding discussion.

The amount of exposure for any given type of fiber should be addressed in terms of three categories. It should be based on an index of intensity-adjusted duration of exposure. In the European study the index may be the sum over the three technological phases of duration of exposure (in the distant period) in a given phase multiplied by an intensity-of-exposure coefficient for that phase. In the American study, in turn, the index may be their "integrated exposure" measure. In the Canadian study, total duration of exposure in that period would have to do. Whatever the index, the cut-off points between low, intermediate, and high exposure should be chosen more or less as the first and second tertiles of the distribution of the values of the index.

For any given stratum (based on age, calendar time, and region), then, the data consist of the observed numbers of cases (O_{1j}, O_{2j}, O_{3j}) and their corresponding population-times of observation (T_{1j}, T_{2j}, T_{3j}) for low, intermediate, and high exposure, respectively, together with the corresponding reference incidence-density of death from lung cancer (I_{0j}); and these imply the corresponding expected numbers $E_{ij} = I_{0j}T_{ij}$, $i = 1, 2, 3$.

Mutually standardized SMR values for the three levels of exposure, based on all of the strata, may then be derived as

$$SMR_i = [\Sigma_j W_j (O_{ij}/T_{ij})]/[\Sigma_j W_j (E_{ij}/T_{ij})] \quad \text{(equation 1)}$$

$$= (\Sigma_j W_j{}^* O_{ij})/(\Sigma_j W_j{}^* E_{ij}). \quad \text{(equation 2)}$$

In what has been done according to the study reports (6—8), the weights W_j have been considered (implicitly) as equal to T_{ij}, so that $W_j{}^* \equiv 1$; but when $W_j = T_{ij}$, the weights for the rates (observed and expected) remain specific for the particular amounts of exposure, and they are, thus, standardized only within the SMR values, not among them. Proper weights are the same across the amounts of exposure; and ideal weights are, in addition, proportional to the amounts of comparative information. In these terms, a first improvement in the weights would be to take them as

$$W_j = (1/T_{0j} + 1/T_{1j} + 1/T_{2j})^{-1}, \quad \text{(equation 3)}$$
$$W_j{}^* = [T_{ij}(1/T_{0j} + 1/T_{1j} + 1/T_{2j})]^{-1}.$$

Yet better weights are

$$W_j = I_{0j}(1/T_{0j} + 1/T_{1j} + 1/T_{2j})^{-1}, \quad \text{(equation 4)}$$
$$W_j{}^* = I_{0j}[T_{ij}(1/T_{0j} + 1/T_{1j} + 1/T_{2j})]^{-1}.$$

The variance of SMR_i may be estimated as

$$\hat{V}_{SMRi} = [(SMR_i)\Sigma_j (W_j{}^*)^2 E_{ij}]/\{[\Sigma_j (W_j{}^*) E_{ij}]^2\}, \quad \text{(equation 5)}$$

and $100(1-\alpha)$ % two-sided confidence limits may then be derived as

$$\exp[\log(SMR_i) \pm X_\alpha (V_{SMRi})^{1/2}/SMR_i], \quad \text{(equation 6)}$$

where X_α is the square root of the $1-\alpha$ fractile of the chi-square distribution (1 degree of freedom).

Testing of the significance of the trend in the SMR over the three levels of dose may be based on weighted regression (5, pp 207—209).

Considering that all of these SMR values will, again, be confounded by socioeconomic status and that the amount of this confounding will depend on age and calendar time, it will also be essential for their interpretation to provide data on the distribution of the exposed segment of the study base (population-time) over the strata on the basis of age and calendar time (collapsing the elementary strata over geographic regions), separately for each type/amount of exposure. It will also be good to provide the observed and expected numbers of cases by these (partially collapsed) strata to assist the judgments and to provide for supplementary analyses by reviewers of the results.

Regression analyses

Whereas the SMR analyses draw from comparisons between exposed (sub)cohorts and the geographically matched "general population," they involve the following drawbacks: (i) for population-time relatively close to the time of first employment, they involve the healthy worker effect, (ii) for all population-time they involve confounding by socioeconomic status, and perhaps by smoking in addition, (iii) they rely on relatively superficial data (in terms of which all members of the cohort have been characterized), and (iv) they suffer from the statistical inefficiency inherent in stratified analyses in the absence of matching (as is the case when different amounts of exposure are compared; see reference 5, pp 216—217), and also inherent in exposure definitions of the sort of a given type of exposure only (5, pp 33—34).

The recommended focus on exposures at least, say, 20 years prior to outcome classification obviates the first problem, and the recommended way or dealing with different amounts or exposure obviates the consequences of the second one in most of the analyses. Yet the proposed reanalyses for SMR values leave, as has already been noted, all of them subject to confounding by socioeconomic status, and the third and fourth problems are inherent in SMR analyses.

All of these problems are resolved, to varying degrees, if "the general population" is omitted as the reference population and, instead, (i) contrasts (based on exposure) are formed within the cohort (its blue-collar segment), (ii) superficial data on the entire cohort are replaced by more-detailed data on its cases and on a sample of its time course (matched to the case series on the stratification factors), and (iii) stratified analyses are replaced by ones based on regression models (incorporating the stratification factors, for example).

On the other hand, this alternative to the SMR approach is relatively uninformative if the variability of exposure within the cohort is small — prone to arise as a result of a relative lack of experience with nonexposure (in the etiologically relevant time period) within the cohort.

It follows that the SMR analyses should be supplemented by such regression analyses (20) within each of the three cohorts. For, even if a lack of variability in exposure were to be a problem, it would be well manifest in relatively wide confidence intervals for the qualitative contrasts, whereas the "dose-response" analyses cannot but gain in precision.

New data related to the cohorts

The most relevant data related to the three cohorts with respect to lung cancer mortality in relation to fiber exposure in a suitably distant period of time are wanting as of now, as has already been noted.

The most obvious, though not the most important, shortcoming concerns the precision afforded by the currently available data. For each of the three particular types of fiber the confidence limits for the SMR are still wide. A partial solution to this problem is ex-

tension of the cohorts' follow-up for lung cancer mortality. If a five-year extension were to be effected, it can be confined to those who at the conclusion of the previous follow-up represented experience more than 16 years after first employment in MMMF production.

In this follow-up, the first concern should be identification of all cases of death from lung cancer, ultimately with the use of the same information used in population vital statistics. However, each case thus identified will need to be classified as admissible or inadmissible, and discarded if inadmissible. Inadmissible cases include, first, those who meet any of the exclusion criteria given in the section SMR Reanalyses as applied to the time of death. In addition, excluded should be those who can be inferred to have been appreciably exposed to extraneous agents on account of their type of occupation, notably furnace operators and curing oven operators before automation of the ovens.

For each admissible case, some five admissible reference subjects, matched (exactly) for age, calendar time and plant, should be drawn randomly from among the survivors in the cohort (at the age and time of the case's death) — with inadmissibility defined identically with that of the cases.

For each admissible case and referent the work history should be abstracted, blindly as to the case-noncase status, in all accessible detail with a view not only to the type of fiber but also to fiber diameter, use of oil as a dust suppressant, and rate of production in the MMMF plant, as well as relevant exposures in work outside MMMF production. These elements should then be translated to a refined index of intensity and duration of exposure in the relevant time periods, drawing from the work of Dodgson et al (21) and that already under way in the context of the American study (7).

If, in the light of the reanalyses outlined under SMR Reanalyses, it is deemed that comparison with "the general population" is helpful (on account of limited availability of nonexposure over 20 years ago within the cohorts), then the relevant rates of this kind should be abstracted as well. However, given the problem of confounding by socioeconomic status, every effort should be made to obtain rates (of lung cancer mortality) specific for industrial workers, separately for skilled and unskilled workers among them. Invocation of this type of reference information requires that also population-time of follow-up, by category of exposure within the strata, be derived for the extension of the cohorts' follow-up.

Given the refinements in this extension of follow-up, these refinements should also be extended backward to the experience already covered, to allow for proper pooling of evidence over time. How far back to go needs to be judged with a view both to the amount of information and to its validity. The amount of information in any given (marginal, early) period of calendar time must be viewed in terms of the (null) expected number of cases exposed in the etiologically relevant period, in proportion to the expected number from subsequent experience. The validity, in turn, is mainly a matter of accuracy of work histories and possibly also of the availability of reference rates specific for industrial workers. In the setting of this cut-off point in retrospective calendar time, it is to be borne in mind that, apart from relevance, validity dominates over precision. It is better to be imprecisely right than precisely wrong.

In these refinements, the acquisition of data on the smoking histories of the cases and the base sample from the cohorts would be highly desirable for the purpose of exploring, and possibly controlling, confounding by it if it could be done with the required accuracy. (See Validity of Content under Requirements for Informativeness.) Chances for attaining such accuracy are remote even in respect to follow-up that is yet prospective (newest extension), to say nothing about the experience that is already retrospective. Since poor data on smoking serve only to confuse the issue, it is recommended that these histories not be pursued and that, instead, socioeconomic status be controlled by means of intracohort analyses and the use of reference rates specific to industrial workers, as stressed.

New studies

The focus, up to now, on the three production-worker cohorts has sprung from the original idea of focusing on persons representing appreciable exposures a suitably long time ago and from an appreciation of the efficiency inherent in building, in the context of extensions of follow-up, on work already accomplished. It is to be recognized, at the same time, that exposures in the late technological phase are no longer high and thus not very informative for testing the hypotheses concerning MMMF as a cause of lung cancer. This development serves to diminish the utility of extended follow-up of the cohorts.

This situation raises the question of whether it is possible to identify cohorts which, in the near future, would represent higher levels of exposure in the suitably distant past than MMMF production workers (active or retired) do. Blowing wool insulators might soon become a useful population to study, barring unsurmountable problems in forming such a cohort in an unbiased way, and other types of cohorts probably would have potential as well.

It follows that sponsors of epidemiologic work on the safety of MMMF (notably JEMRB and TIMA) should sponsor pilot studies on the feasibility of forming informative new cohorts and, in the second phase, float a request for proposals of actual work on such cohorts. In the evaluation of such proposals, care should be taken to assure that the proposals involve the recruitment of, or deployment of a priori existing, reference cohorts consisting of workers in particular

unexposed occupations. For any given exposed cohort there should be more than one reference cohort of a size at least equal to that of the exposed cohort; and all of these should represent comparability with the exposed cohort in terms of a priori judgments regarding the relevant issues. The availability of several, sizable reference cohorts provides for the assessment of their homogeneity of risk and, thus, of the tenability of the a priori judgments.

CONCLUDING REMARKS

As has been shown in this review, the currently available epidemiologic evidence is inadequate for testing the hypothesis that MMMF exposure constitutes a hazard in respect to lung cancer.

The evidence derives from work that accords with the traditional principles of epidemiologic research in general (22), and of occupational health epidemiology in particular (23), but it does not measure up to the more stringent requirements of modern epidemiologic research (5, 24), outlined in the section Requirements for Informativeness of this review. For critical rethinking of the principles of epidemiologic research on occupational cancer risks, the central topic should be, we suggest, the conditions for appropriateness of the traditionally common basic approach to such research. In this process, the point of departure is, quite properly, the enrollment of an occupationally exposed cohort. Some problems arise from the common practice of utilizing its retrospective experience as to the occurrence of the cancer (or death from it). But the main problems lie with the routine of contrasting this experience with that in the open (dynamic) "general population." As has been illustrated in this review, and argued elsewhere (eg, 5), serious problems tend to be associated with this type of contrast, the "healthy worker effect" being a well familiar, yet only one, manifestation of these. This type of contrast remains ingrained in occupational epidemiology, we believe, mainly on the grounds of the historical and more demographic than epidemiologic paradigm of SMR statistics for various occupations, provided by central registries of deaths, originally in Great Britain. Proper paradigms are found in laboratory and clinical science (5, 24), a manifestation of which is the absence of the concept of the "sick patient effect" from the latter. In these terms, an occupationally exposed cohort is to be contrasted to a comparable unexposed cohort with a view to coexposures, type of subject, and accuracy of outcome information.

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